Preliminary Comments on the ISA from Dr. Philip Goodrum

Comments on Chapter 4

Please comment on the adequacy of these and other changes in responding to the Panel's comments. Please provide comment on revisions that may further improve the utility of this chapter for interpretation of health evidence in subsequent chapters.

In general, EPA was largely responsive to comments from the CASAC committee on Chapter 4, and suggestions to better integrate Chapters 3 and 4. Specific comments are given in the table below for each of the comments and recommendations that CASAC provided on ISA Version 2.

CASAC's Comments on ISA Version 2		**Comments on ISA Version 3**
1	Additional synthesis and summary of information is needed on the following	
1a	Section 4.1 – example, Section 4.1.3.3 (Dietary Lead Exposure) – Information is factual, but the reader will benefit from more interpretation, context, and summary. Include additional discussion to explain the importance and impact of the reviewed data to the ISA. This recommendation can be generalized to all chapters of the ISA document – EPA should review each section and determine if, in addition to summarizing the information/data available, the implications of this information is also conveyed.	Text was added to effectively convey the implications of the exposure pathway-specific summaries. For example, Dietary Pb exposure is discussed in 4.1.3.3. A paragraph was added (p.4-28, lines 19-32) to tie together multi-source contributions to Pb in food items.
1b	Section 4.1.1, p. 4-6 – The additional paragraph is helpful at presenting quantitative estimates of % contribution of air Pb to blood Pb. Include a table that summarizes this information, distinguishing between estimates based on modeling (e.g., IEUBK) and empirical studies. Then add text to synthesize/summarize this information with specific focus on the importance of changes in these % contribution estimates over time, or as a function of the low end vs high end blood leads.	Addition of Table 4-2 summarizes % contribution to median and 95th percentile blood Pb, assuming GSD = 2.1. The text should further discuss the implications of the modeling results presented in this table – specifically, increasing the air Pb from 0.14 to 0.87 µg/m^3 (a factor of 0.7) yields an increase in blood Pb of 0.2 µg/L for the median (slope =0.27 µg/L per µg/m^3) and 0.7 µg/L (0.96 µg/L per µg/m^3).
1c	Add a section that relates estimates of blood Pb / air Pb slopes to the original goals of the ISA as presented in the Integrated Review Plan, which called for an uncertainty analysis that provides a foundation to review the NAAQS. For example, the	See comments on 1b.

	ISA can demonstrate how a particular slope factor translates into a corresponding change in blood Pb at the GM and 95th percentile of the distribution assuming a lognormal distribution with GSD =1.6 (a model adopted in IEUBK).	
2	Additional discussion and perspectives on the relevance of information as presented is needed:	
2a	Chapter 4 leaves the impression that from a multipathway exposure perspective, direct inhalation of air Pb is generally a relatively minor contributor to total dose compared to soil/dust ingestion, diet, water ingestion and other routes of exposure (although some exceptions are noted, such as populations living in the vicinity of an airport). This may raise questions regarding the interpretation of the blood Pb / air Pb slopes, or the potential for a reduction in NAAQS to have a meaningful effect on blood Pb. Chapter 3 provides a more explicit discussion of the correspondence between air Pb and multiple exposure media (beyond air itself). Need better linkage between Chapter 3 and Chapter 4.	Pages 415-416, addition of new paragraphs explain some of the uncertainties associated with developing slope estimates from empirical data, appropriately concluding on a neutral tone "..[uncertainties] may lead to both positive and negative biases in the [slope factor] estimates from individual studies. New sections on particle size help to make the point that particle size governs exposure routes and that inhalation is not the only exposure route for Pb in air.
2b	Section 4.2.1, p. 4-30, lines 24-28 – expand this discussion to include the concept that time-integrated blood Pb reflects an aggregation of the biological processes that includes both recent Pb bioavailability/absorption as well as inputs from soft tissue and bone.	This points were added.
2c	Figures 4-8; 4-9; and 4-11 – the simulations are very informative and help to illustrate the temporal profile of Pb in blood, bone, and overall body burden. The text (p. 4-63) indicates that the simulations represent an exposure scenario in which a child experiences "..a constant Pb intake (from age 2-5) via ingestion… followed by an abrupt decline in intake." Additional details regarding the exposure/dose would be useful - specifically what constant Pb intake was administered, and when intake was abruptly reduced – was this set at zero or some non-zero baseline? Further clarification on the relevance/interpretation of the time averaging would be useful since it is unclear how the reduction in variance attributable to the averaging can be related to the experimental data. Consider removing the	These additional notes were added.

	time-weighted average blood Pb panel.	
2d	Figure 4-22 – very helpful addition to demonstrate the various slopes, particularly to emphasize the differences in the model selection (e.g., log-log, log-linear, etc). The shapes of the response curves are very divergent at low air concentrations. Given the focus of the NAAQS is at the low end of the air Pb range presented, EPA should 1) comment on the challenge of estimating the low-end of the curves (i.e., < 0.2 µg/m^3) from data collected, and 2) comment specifically on the magnitude of difference in estimates and representativeness of the statistical models applied to empirical data. EPA should conduct an independent analysis of the underlying studies and determine if a common model can be used to describe all the datasets. Then, tie this back to estimates of expected change in blood Pb associated with change in NAAQS (see 1(c) above).	The figures are still included, but I did not see this additional discussion included in Version 3.
2e	The ISA presents a range of blood Pb / air Pb slope factors without pinpointing a subset of estimates that may be more relevant to the objectives of the REA. To the extent that EPA has already identified a "best estimate" of a slope factor, or a range of best estimates, this information should be included in the ISA, accompanied by a discussion for the rationale that supports the selection.	Paragraph added to p. 4-130
2f	Comment on the importance of errors associated with estimates of particle size distributions from historical Pb TSP measurements. How does this uncertainty likely contribute to 1) estimates of air Pb / blood Pb slopes; 2) estimates of predicted blood Pb from epidemiological data; and 3) corresponding uncertainty in predicted change in blood Pb associated with reduction in air Pb (see 1(c) above).	Additional discussion on TSP was added.
2g	Section 4.1.1 presents the conceptual model for a multi-pathway assessment. Page 4-6 (lines 8 to 34) discusses the relevance of particle size distributions for inhalation and soil/dust ingestion exposure pathways. The first sentence (line 8) states: *Particle size of Pb-PM is relevant to transport through various media leading to exposure*. Restate this or expand the introduction to emphasize that all particle	Chapter 3 and 4 include this overall message.

	sizes are relevant to lead exposure assessment in general, and to understanding the air Pb / blood lead relationship specifically.	
2h	Historical perspective on change in Pb sources over time associated with change in blood Pb – Chapters 3 and 4 remained somewhat biased towards gasoline Pb phase down (e.g., Section 3.7.1; Section 4.4.1, p. 4-78, introductory paragraph); also emphasize the role of reductions in emissions in the vicinity of point sources as presented subsequently (e.g., pp. 4-84 to 4-86).	Concepts are included on page 3-28.
3	The following contradictions need to be addressed:	
3a	Clearance rates for blood Pb – the text (e.g., 4-62) suggests that the rate of change may be slow following cessation, such that blood Pb will remain elevated years after exposure ends. Yet, the narrative discussion at the top of page 4-67, and the model simulations in Figure 4-11 (ICRP modeling) suggests exactly the opposite – a rapid decline in blood Pb following cessation. EPA should provide more description regarding model assumptions (e.g., how was baseline exposure factored in?), and comment on whether this relationship may differ for higher blood Pb that corresponds with adult occupational exposure. Literature that provides empiric observation for change in blood lead following cessation of exposure that resulted in moderate elevations (e.g., blood Pb in the 10 to 25 ug/dL range) for various time durations should be discussed (if available).	Additional discussion was added on clearance rates.
	% Pb in blood - Page 4-39 (line 23) and 4-120 (line 22) report that 1% of body burden is in blood, whereas 4-49 (line 12) reports 5%.	In Section 4.3 (Biomarkers, page 4-52, line 23), 5% was changed to 1% for consistency